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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,683	10/02/2003	David Borcherding	USA3960 US CNT	8394

5487 7590 10/17/2005

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/677,683	BORCHERDING ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED .(35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/998,976* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term "hyperproliferative" in claim 3 is unclear. The specification does not contain a clear definition for the term. A proliferative disorder, in its broadest sense, is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. However, the term is often not used in that broadest sense. Moreover, the claim has hyperproliferative, which the examiner presumes is some special subset of proliferative, although again, it is unclear what that subset is.
2. The inclusion of asthma in claim 14 makes no sense. The claim is dependent on claim 3, which requires "hyperproliferative", but asthma is not normally thought of as a

hyperproliferative disorder, unless applicants are using some unusually broad definition of "hyperproliferative".

3. Similarly, "allograft rejection" is not an autoimmune disease. It deals with the rejection of a graft from another person.. It is also not a hyperproliferative disorder. Indeed, it is arguably not even a disease at all; but rather the body doing what it is supposed to do, rejecting not-self tissue.
4. Claim 20 appears to be the same as claim 16. Preventing apoptosis and protecting from apoptosis are the same thing.
5. The scope of claim 12 is unclear. It is drawn specifically to hyperproliferative disorders which are not neoplasias. However, there is no clear line between hyperproliferative disorders which are and are not neoplasias, because the definition of a neoplasm and of a hyperproliferative disorder is fairly similar. The specification provides no guidance on how to draw such a line. A neoplasm is simply abnormal new growth, a term which isn't really narrower than hyperproliferative. Thus, restinosis, recited in claim 13 takes the form of abnormal new growth.
6. The scope of claim 22 is not clear. What exactly qualifies as a CDK is not always agreed upon. Does it have to have the form of "CDK" followed by a numeral? Even there, the names can change over time. Thus, what once called Tau PK II is now called CDK6. What was until recently called PISSLRE is now (sometimes) called CDK10. What about the "CDK-like" kinases, which have CDK at the start, but not a numeral next, i.e. CDKL1 (also called KKIALRE) and CDKL2 (also called P56 or KKIAMRE)? Further, what about the "PCTAIRE" group (PCTAIRE1, PCTAIRE2, PCTAIRE3)? What about STK9 (serine/threonine kinase 9)? These have been (sometimes) classified with the

CDKs, but do not have CDK as part of their name? Does it includes non-mammalian CDKs such as PHO85, SSN3 and KIN28 ?

7. Claim 23 is not correct. These are not actually CDKs. These are complexes of CDKs with activators (the activator is the material after the slash).
8. Also, the last choice has "cyclin D" but in fact, there is no such thing. There are cyclins D1, D2 and D3.
9. The "substituted by a nitrogen atom" of third line below the page 5 structures is not correct. A N atom requires three bonds; no carbon in any of these rings has more than one H to displace. Did applicants mean "nitro"? Amino? Replaced by a N? For whichever choice is made, applicants must show that one of ordinary skill in the art would have known that this choice, and not another, was intended.
10. The choice of X as =O is not possible for the same reason: No carbon has two hydrogens to be replaced. Moreover, X is depicted clearly as monovalent in the structures where it appears on the top of page 5.
11. The "saturated or unsaturated" for alkyl is not correct. An alkyl by its very nature cannot be unsaturated. Alkyl is a group of the formula -C_nH_{2n+1}, as such it cannot be unsaturated.
12. "Heterocyclic" (e.g. in the NR5 definition) is indefinite. What is the number and nature of the heteroatoms? Can the ring be fused or spiroconnected to another ring, and if so, what kind of ring? Can the ring be bridged? Unsaturated? Cf. *In re Wiggins*, 179 USPQ 421, 423.
13. The choice of "an unsubstituted N" for NR6 does not make sense. That would give a N with just two bonds, i.e. –N-. How is that possible?

14. The term "mixed type of neoplasm" is unclear. Is this the same thing as "mixed neoplasm", or is it something broader?

15. Moreover, even if the term is designed as "mixed neoplasm", that term has no fixed meaning. It is often used in the sense of neoplasm derived from both epithelial or mesenchymal tissues, sometimes in the sense of a tumor from more than one of the major types, such as carcinosarcoma, and sometimes any tumor which appears to have two different types of neoplasms present, regardless of their actual nature.

16. In addition, claim 11 is unclear. This seems to be saying that e.g. Hodgkin's disease is a mixed neoplasm, which it is not. There is a type called "Mixed cellularity Hodgkin's lymphoma", but that isn't really a mixed neoplasm in the ordinary sense. Thus, the meaning of claim 11 is unclear.

17. The last two X choices in claim 1 are unclear. Is the "alkyl" a linker between the CO and the ring? If so, it should be "alkylene". Likewise in other places.

18. The use of "C0" for alkyl (see last page 5 choice and first one on page 6) is mistaken. An alkyl group by its very nature must have at least one carbon.

19. The word "cervis" in claims 7-8 should be "cervix".

20. The intention of claim 10 is unclear. There are the only two types. So how does claim 10 limit claim 5?

21. The sixth from the last line of claim 1 has "where phenyl is...." Which phenyl is this? Is it any phenyl ring? Or only a phenyl which is said to be optionally substituted? Does it include the fused phenyl rings seen in the definition for W?

22. The second through fourth words of claim 20 should be deleted as duplicative.

23. Some of the variables have circular definitions. The definition for R4 and R5 includes alkyl groups which can be substituted by X, but the definition of X includes choices having R4 and R5 in them, which just starts the cycles again. Similarly, in the last lines of the claim, phenyl can be substituted by substituents having R4 and R5, but those substituents can be substituted by X, which can be substituted phenyl, which starts the cycle again.

Claims 3-22, 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.
The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Doe to the deeply nested nature of the Ra variable (Ra can be NR1R3, where R1 can be a choice with Q and two W groups, and Q can have another R3 substituent, and W can be assorted rings with B (which has the R6 substituent) and

several X substituents, which X substituents can have R4 and R5 substituents on them, variables which have very broad definitions), the claim covers millions if not billions of compounds.

(b) Scope of the diseases covered. The coverage is colossal.

A. A proliferative disorder, listed in e.g. in claims 3 and 12 is anything that causes any abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such a term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, and polyps. In addition, it embraces various non-cancerous proliferative disorders such as certain types of restenosis, vascular smooth muscle proliferation associated with atherosclerosis, glomerular nephritis, pulmonary fibrosis, clonal proliferative disorders including the various Myelodysplastic Syndromes (the assorted Refractory Anemias, Ph-Chromosome-Negative Chronic Myelocytic Leukemia, Chronic Myelomonocytic Leukemia and Agnogenic Myeloid Metaplasia) and the Myeloproliferative Disorders (Chronic myelogenous leukaemia, which exists in adult and juvenile forms; Polycythemia vera;. Agnogenic myeloid metaplasia and Essential thrombocythemia). It includes certain types of abnormal wound healings. It covers numerous types of abnormal angiogenisis e.g. in certain eye diseases (such as neovascular glaucoma, diabetic retinopathy, retinopathy of prematurity, retrolental fibroplasias, and age-related and certain other types of macular degeneration), Rosacea, some neurodegenerations, respiratory distress in the premature infant, some problems in embryonic development, and atherosclerosis. It includes the

myeloproliferative disorders (such as primary polycythemia, primary (essential) thrombocythemia, chronic myelogenous leukemia and myleofibrosis). Also included are numerous Plasma cell dyscrasias, such as Multiple myeloma, Smouldering Myeloma, monoclonal gammopathy of unknown significance (MGUS), solitary plasmacytoma of bone (SPB), asymptomatic myeloma, Waldenström's macroglobulinemia, Solitary extramedullary plasmacytoma, Primary Amyloidosis, POEMS syndrome, and the three heavy-chain diseases). It also includes an assortment of skin disorders, such as psoriasis, atopic dermatitis, allergic contact dermatitis, epidermolytic hyperkeratosis, palmoplantar Pustulosis, lichenified eczema, seborrhoeic dermatitis and the keratinization disorders (including assorted ichthyoses, keratosis pilaris, keratosis follicularis, tylosis, "knuckle pads", corns, assorted callosities, and numerous keratinization disorders found in dogs and cats). Also included are LAM (Lymphangioleiomyomatosis, a smooth muscle proliferative disorder of the lungs) rheumatoid arthritis and even Alzheimer's Disease. It covers most inflammatory and immune disorders. Indeed, almost anything that the body grows --- skin, blood cells, nerves, plasma, muscles, the vascular network, can grow too fast, or in a manner too undifferentiated.

B, Cancer, covered by claim 4. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body.

C. Leukemia is covered by claim 4, and claim 5 has a list which includes chronic leukemias and the two major acute leukemias. Leukemia is any malignant neoplasm of the blood-forming tissues. Leukemia can arise from many different sources. These includes viruses such as EBV, which causes Burkitt's lymphoma, and HTLV-1, linked to certain T cell leukemias. Others are linked to genetic disorders, such as Fanconi's anemia, which is a

familial disorder, and Down's Syndrome. Other leukemias are caused by exposure to carcinogens such as benzene, and some are actually caused by treatment with other neoplastic agents. Still other leukemias arise from ionizing radiation, and many are idiopathic. Leukemias also differ greatly in the morphology, degree of differentiation, body location (e.g. bone marrow, lymphoid organs, etc.) There are dozens of leukemias. There are B-Cell Neoplasms such as B-cell prolymphocytic leukemia and Hairy cell leukemia (HCL, a chronic leukemia). There are T-Cell Neoplasms such as T-cell prolymphocytic leukemia, aggressive NK cell leukemia, and T-cell granular Lymphocytic leukemia. There are different kinds of acute myeloid leukemias, acute promyelocytic leukemias, acute myelomonocytic leukemia, chronic myelomonocytic leukemia, acute monocytic leukemias, and erythroleukemias. There is also acute megakaryoblastic leukemia, acute promyelocytic leukemia, Multiple Myeloma, lymphoblastic leukemia, hypocellular acute myeloid leukemia, Ph-/BCR- myeloid leukemia, acute basophilic leukemia, and acute myleofibrosis. Chromic leukemias include chronic lymphocytic leukemia(CLL, which exists in a B-cell and a T-cell type), prolymphocytic leukemia(PLL), large granular lymphocytic leukemia (LGLL, which goes under several other names as well), chronic myelogenous leukemia(CML), chronic myelomonocytic leukemia, chronic granulocytic leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and many others. No compound has ever been found effective generally against leukemias because they are simply too diverse.

D. Claim 5 covers carcinoma, and claim 7 lists a broad range of major carcinomas, and claim 8 has a similar list of adenocarcinomas. A carcinoma, (including adenocarcinomas and squamous cell carcinomas) is any cancer that arises from epithelial cells. Such cancers

can occur in almost every part of the body, and there are dozens and dozens of different types.

The most important family of Carcinomas of the skin are the Basal cell carcinomas (BCC), including Superficial BCC, Nodular BCC (solid, adenoid cystic), Infiltrating BCC, Sclerosing BCC (desmoplastic, morpheic) , Fibroepithelial BCC, BCC with adnexal differentiation, Follicular BCC, Eccrine BCC, Basosquamous carcinoma, Keratotic BCC, Pigmented BCC, BCC in basal cell nevus syndrome, Micronodular BCC. Another important family is the Squamous cell carcinomas (SCC) which include Spindle cell (sarcomatoid) SCC, Acantholytic SCC, Verrucous SCC, SCC with horn formation, and Lymphoepithelial SCC, along with less well classified SCCs such as Papillary SCC, Clear cell SCC, Small cell SCC, Posttraumatic (e.g., Marjolin ulcer) and Metaplastic (carcinosarcomatous) SCC. Another family is the Eccrine carcinomas including Sclerosing sweat duct carcinoma (syringomatous carcinoma, microcystic adnexal carcinoma), Malignant mixed tumor of the skin (malignant chondroid syringoma), Porocarcinoma, Malignant nodular hidradenoma, Malignant eccrine spiradenoma, Mucinous eccrine carcinoma, Adenoid cystic eccrine carcinoma, and Aggressive digital papillary adenoma/adenocarcinoma. Other carcinomas of the skin include Epidermal carcinomas, Paget disease, Mammary Paget disease, Extramammary Paget disease Adnexal carcinomas, Apocrine carcinoma, Sebaceous carcinomaTricholemmocarcinoma and Malignant pilomatricoma (matrical carcinoma).

Carcinomas of the Liver include Hepatocellular carcinoma, Combined hepatocellular cholangiocarcinoma, Cholangiocarcinoma (intrahepatic), Bile duct cystadenocarcinoma and Undifferentiated carcinoma of the liver.

The carcinomas of the extrahepatic bile ducts are of numerous types, including carcinoma in situ, Adenocarcinoma, Papillary adenocarcinoma, Adenocarcinoma (intestinal-type), Mucinous adenocarcinoma, Clear cell adenocarcinoma, Signet ring cell carcinoma, Adenosquamous carcinoma, Squamous cell carcinoma, Small cell carcinoma (oat cell carcinoma) and undifferentiated carcinoma of the extrahepatic bile ducts.

Renal carcinomas include papillary renal cell carcinoma, conventional-type (clear cell) renal carcinoma, chromophobe renal carcinoma and collecting duct carcinoma.

Carcinomas of the prostate are usually adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma, basal cell carcinoma, signet-ring cell carcinomas and others.

The non-small cell lung carcinomas include a large number of Adenocarcinomas which include the Bronchioloalveolar carcinomas (Nonmucinous, Mucinous, and Mixed mucinous and nonmucinous or indeterminate cell type), Acinar, Papillary carcinoma, Solid adenocarcinoma with mucin, Adenocarcinoma with mixed subtypes, Well-differentiated fetal adenocarcinoma, Mucinous (colloid) adenocarcinoma, Mucinous cystadenocarcinoma, Signet ring adenocarcinoma, and Clear cell adenocarcinoma. There are also Squamous cell carcinomas, which can be Papillary, Clear cell, Small cell and Basaloid. There are also the Large cell carcinoma, which include Large-cell neuroendocrine carcinoma, Combined large-cell neuroendocrine carcinoma, Basaloid carcinoma, Lymphoepithelioma-like carcinoma, Clear cell carcinoma, and Large-cell carcinoma with rhabdoid phenotype. In addition there are also the carcinomas with pleomorphic, sarcomatoid or sarcomatous elements, including Carcinomas with spindle and/or giant cells, Spindle cell carcinoma, Giant cell carcinoma, Carcinosarcoma andPulmonary blastoma. The non-small cell lung carcinomas also include

Adenosquamous carcinoma, the Carcinoid tumor (both typical Carcinoid and atypical Carcinoid) as well as carcinomas of salivary-gland type, including mucoepidermoid carcinoma and adenoid cystic carcinoma.

Penile carcinoma is usually a squamous cell carcinoma, but there is also Penile clear cell carcinoma and Sarcomatoid carcinoma.

Carcinomas of the central nervous system include Choroid plexus carcinoma, Pituitary carcinoma, Embryonal carcinoma, Choriocarcinoma, and others.

The above lists are merely representative. There are also carcinomas of the bone, breast, GI tract, ovaries, cervix, eyelids, etc.

E. Sarcomas are listed in claim 9, and in mixed form in claim 11. Sarcomas are cancers in which the cancer cells arise from or resemble normal "connective tissues" cells in the body. These tumors occur at nearly all sites within the body including the head and neck, torso, retroperitoneum, pelvis, and limbs, and are quite varied. Categories and types include Liposarcomas, Leiomyosarcomas (including uterine sarcomas)which can arise nearly anywhere in the body, Rhabdomyosarcomas (of which there are many kinds, e.g. paratesticular rhabdomyosarcoma, and Pleomorphic rhabdomyosarcoma (PRMS)), Synovial Sarcomas, which can also arise in almost any location in the body, Angiosarcomas (e.g. Liver angiosarcoma), Liposarcoma (including intra-muscular lipoma, angiolipoma and spindle cell sarcoma), Fibrosarcomas (including Fibroma), Malignant Peripheral Nerve Sheath Tumor (MPNST, also called neurofibrosarcoma), Gastrointestinal Stromal Tumor (GIST) also known as GI Stromal Sarcoma, Desmoid Tumor (Musculoaponeurotic fibromatosis), Ewing's Family of Sarcomas (e.g. Ewing's tumor of bone; extraosseus Ewing's (tumor growing outside of the bone); primitive neuroectodermal tumor (PNET);

also known as peripheral neuroepithelioma; and Askin's tumor), Osteosarcoma (also known as osteogenic sarcoma e.g. Malignant fibrous histiocytoma), Chondrosarcomas (including Chondroma), Langerhans cell sarcoma, prostate sarcoma, Histiocytic sarcoma, Cystosarcoma, Osteoma, Kaposi's sarcoma, Reticulum cell sarcoma, Neurofibroma, Hemangioma, Haemangioendothelial sarcoma and Hemangiosarcoma, Neurosarcoma, Epithelioid Sarcoma, Clear Cell Sarcoma of Kidney, Myeloid sarcoma, malignant fibrous histiocytoma (MFH), Benign and Malignant Schwannoma, Lymphangiosarcoma, Neurilemmoma, Interdigitating dendritic cell sarcoma, Leydig cell sarcoma (LTW), and many others.

These tumors, which can occur in soft tissue or in bones or in blood, are so diverse that it is contrary to medical understanding for them to be treated generally by any one agent, and in fact, no such agent exists. Indeed, sarcomas generally speaking do not respond particularly well to primary chemotherapy, especially as compared to many other types of tumors. Instead, sarcomas are more frequently treated with surgery, or radiation, or even regional hyperthermia (RHT), and Photodynamic therapy (PDT).

F. Melanoma, covered by claim 10, is a general type of cancer, arising primarily from cells which produce melanin, and again is distributed fairly widely in the body, including the regional lymph nodes, skin, liver, lungs, eye, brain, and mucous membranes of the genitalia, anus, oral cavity, colon and other sites. There are a great variety of these.

G. The treatment of "autoimmune diseases" (claim 13) generally would be an unprecedented feat. For a compound or genus to be effective against "autoimmune diseases" generally is contrary to medical science. The "autoimmune diseases" are processes which can take place in virtually any part of the body. There is a vast range of

forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders include multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behcet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), and many more.

H. Claims 15-20 are drawn to prevention of apoptosis, programmed cell death, arising from different causes. Apoptosis arises from a wide variety of mechanisms, some of them very poorly understood. Apoptosis is a normal and routine body process, without with the body would soon die.

I. Claim 21 is drawn to protecting neuronal cells from antineoplastic agents. This is an odd utility, since these compounds are themselves asserted to be antineoplastic agents. Thus these compounds are asserted to protect nerve cells (of which there are many different types) from these very compounds, which makes no sense art all.

J. Claim 22-23 are drawn to inhibiting the effect of CDKs. Again, this is an essential body process; cells cannot be replaced without the activity of CDK and CDK complexes to regulate and thus assure the formation of new healthy cells. Depending of what definition of CDK is used, there could be as many as several dozen of these covered by the claim.

K. Restenosis, or recurrent stenosis, listed in claim 13, is an extremely general term. Stenosis is the narrowing of any canal, orifice, valve, duct, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, etc. There is no such thing as being able to treat such widely diverse problems which arise from different and unrelated sources.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided on page 44 is a range of 0.02-1 mg/kg/day, but this dosage range is of loittle value because it is completely generic. That is, it is the same dosage for all disorders listed in the specification, from asthma to cancer , which is a very substantial range of disorders.

In terms of specific disorders, there are vast pages of disorders listed, especially on apges 7-15 and 21-22.

(4) State of the Prior Art: The claimed compounds are piperidinyl-amino purines, with a particular substitution pattern at several positions. . So far as the examiner is aware , piperidinyl-amino purines have not been successfully used as anticancer agents or for any other utility listed in the specification. .

(5) Working Examples: There are no working examples to the treatment of any actual disease. Table 2 shows inhibition of three CDKs, which cannot be said to be representative of the class as a whole (note that claim 23 is not rejected.) Table 3 lists test results in 3-5 cell lines, and example 4 gives results in xenografts on two cell lines, one an acute leukemia, and one for a prostate cancer.

(6) Skill of those in the art:

I. The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Cancers that affect just a

certain type of structure can be quite varied. Fibromas for example inclde Infantile myofibromatosis, Fibrous hamartoma of infancy. Juvenile hyaline fibromatoses. Infantile digital fibromatoses. Calcifying aponeurotic fibromas. Giant cell fibroblastoma. Ovarian fibroma, Dermatofibroma, myofibroma, myofibromatosis, desmoplastic fibroma, neurofibroma, peripheral odontogenic fibroma, peripheral ossifying fibroma, giant cell fibroma, Chondromyxoid Fibroma, Oral Neurofibroma, Juvenile aponeurotic fibroma (JAF), aggressive infantile fibromatosis (AIF), omental fibroma, Perifollicular fibroma, ameloblastic fibroma, Premalignant Fibroepithelial Tumor (Pinkus Tumor), Periungual fibroma (Koenen tumor), desmoid tumor, tracheal fibroma and many others. Even those that affect just a single organ are often not generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that there could be such a compound. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are

characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy.

II. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Since no compound has shown clinical efficacy against all autoimmune diseases, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. Applicants' specification logically must lack such assay data.

In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in

the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis.

3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that

engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such greatly differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

III. Claim 14 lists some autoimmune disorders, Type 1 diabetes, atherosclerosis and asthma. Such disorders have never been treated successfully with agents that suppress the immune system, and of course there is no evidence at all that these compounds do in fact suppress the immune system. Moreover, atherosclerosis itself is not per se treatable.

IV. One of ordinary skill in the art knows that one of the methods of promoting tumor regression is by inducing apoptosis. These compounds, alleged to be anti-cancer agents, are said to prevent apoptosis. Similarly, autoimmune disorders such as lupus or MS are characterized by too little apoptosis, and so agents which suppress apoptosis would be expected to make matters worse.

V. While sarcomas are listed, sarcomas generally speaking do not respond particularly well to primary chemotherapy, especially as compared to many other types of tumors. Instead, sarcomas are more frequently treated with surgery, or radiation, or even regional hyperthermia (RHT), and Photodynamic therapy (PDT).

VI. With regard to claim 22, although a number of CDK inhibitors have been studied, none of them are active generally against CDKs. Even the non-specific inhibitors flavopiridol and staurosporine are not active against e.g. CDK3 and CDK7 and others. This is mirrored in the fact that there are no proteins which generally activate them either. Indeed, none of the cyclins activate more than three of the CDKs. Thus, it appears that the CDKs are too dissimilar in structure for something to act on them generally.

Moreover, many of the CDKs have an unknown connection to disease. For example CDK8 when associated with cyclin C phosphorylates CTD RNA pol II, but on different site than where CDK7 operates. However, that is not enough to connect the CDK (or CDK7 for that mater) to the treatment of any disease. There are no known inhibitors for these, either natural proteins or synthetic small molecules. CDK3 is even more poorly understood; it isn't even known what substrates (if any) it operates on.

(7) The quantity of experimentation needed: Given the fact that historically the development of new cancers drugs has been difficult and time consuming, and especially in view of factors 1 and 4, the quantity of experimentation needed is expected to be great.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

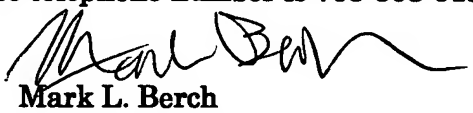
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, and 24-35 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6861524. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims here are just generic to the species already patented in the parent case.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.



Mark L. Berch
Primary Examiner
Art Unit 1624

October 12, 2005